Merck & Co., Inc.
West Point, PA 19486

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July 28, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
Department of Health and Human Services
Room 1-46 Park Building
12420 Parklawn Drive
Rockville, MD 20857

MERCK
Research Laboratories

NDA 20-560: FOSAMAX™ (Alendronate Sodium Tablets)
Citizen Petition: Pediatric Priority List

The undersigned, on behalf of Merck & Co., Inc., submits this petition under section 505A (c) of the Federal Food, Drug, and Cosmetic Act (FFDCA) to request the Commissioner of Food and Drugs to add alendronate sodium (Merck Research Laboratories' Fosamax™) to the priority section (Pediatric Priority List of Drugs Regulated by the Center for Drug Evaluation and Research) of the "List of Approved Drugs for Which Additional Pediatric Information May Produce Health Benefits in the Pediatric Population" ("the List") (Docket 98N-0056, dated May 20, 1998).

A. Action Requested

This petition requests the Commissioner to add alendronate to the priority section of the "List of Approved Drugs for Which Additional Pediatric Information May Produce Health Benefits in the Pediatric Population".

B. Statement of Grounds

On June 16, 1999, the Food and Drug Administration approved Fosamax™ (alendronate sodium) for the treatment of glucocorticoid-induced osteoporosis in men and women receiving glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and who have low bone mineral density. This approved indication for Fosamax™ (alendronate sodium) also occurs in the pediatric population.

Fosamax™ (alendronate sodium) is now considered to be on the "the List" because it is approved for an indication in adults that also occurs in the pediatric population (as defined under "CONTENT OF THE LIST" Docket No. 98N-0056).

Alendronate should now be added to the priority section of the List. In its June 1998 "Guidance for Industry: Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food Drug and Cosmetic Act" (pages 8 and 9), FDA identified the criteria for determining which drugs are to be included in the Priority Section of the List. A drug needs to meet just one of the criteria to be included in the Priority Section of the List. Alendronate's fulfillment of a prioritization criterion is discussed below.

99P-2547

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• Alendronate is an agent which is approved for the treatment of glucocorticoid-induced osteoporosis, an indication for which additional therapeutic options for the pediatric population are needed.

No therapy is currently approved for the treatment of glucocorticoid-induced (or other forms) of osteoporosis in children. Glucocorticoid-induced osteoporosis and associated fractures are a complication of oral glucocorticoid use in children. In addition, since one action of glucocorticoids is to prevent the attainment of peak bone mass, the true burden of illness in many pediatric patients may not be fully manifest until later in life. Glucocorticoid-induced osteoporosis occurs as a result of decreased osteoblast-mediated bone formation and increased osteoclast-mediated bone resorption, resulting in a net excess of resorption over formation.

In addition, glucocorticoid-induced myopathy and muscle weakness may also contribute to bone loss by removing the normal forces on bone that are produced by muscle contraction and may further increase fracture risk by increasing the propensity to fall. Finally, the underlying inflammatory disease (e.g. rheumatoid arthritis), or concomitant drug therapy, may also contribute to osteoporosis in patients treated with glucocorticoids.

The adverse effects of glucocorticoids on bone turnover have been documented in a number of longitudinal studies using different biochemical markers, alone or in combination, in children receiving glucocorticoids for a variety of diseases, including inflammatory bowel disease, asthma, and acute lymphoblastic leukemia.

Osteoporosis and associated fractures are a common complication in children (and adolescents) receiving supraphysiologic doses of glucocorticoids, for several reasons. First, childhood and adolescence are a time of high bone turnover, and glucocorticoids, by decreasing osteoblastic bone formation and increasing osteoclastic bone resorption, can produce a marked imbalance between the two processes, resulting in a negative calcium balance. Second, the use of glucocorticoids during adolescence may also prevent the patient from reaching his/her peak bone mass by decreasing bone modeling (1), due to the potent inhibitory effect of glucocorticoids on bone formation and, possibly, their inhibitory effect on GH secretion (2). Finally, a number of pediatric disorders for which glucocorticoids are prescribed such as juvenile chronic arthritis (mostly rheumatoid) and inflammatory bowel disease are independently associated with osteoporosis.

Asthma, juvenile rheumatoid arthritis, and inflammatory bowel disease are the most common chronic diseases that often require long-term glucocorticoid therapy. The prevalence of asthma is approximately 75 cases per 1,000 American children 16 years or younger, resulting in a total number of approximately 5.3 million affected children (3). However, although a relatively large number of asthmatic children may require treatment with glucocorticoids, only a very small proportion (approximately 1%) receives chronic therapy with oral glucocorticoids (4). In most cases, inhaled glucocorticoids are used, at relatively small doses, which have not been unequivocally associated with significant bone loss or increased fracture risk (5).

Juvenile rheumatoid arthritis is much less frequent than asthma, with a prevalence of about 134 cases per 100,000 American children ≤ 16 years, or approximately 90,000 children (6). Approximately 30-40% of these children will require treatment with glucocorticoids, which are usually the last therapeutic resort. The prevalence of inflammatory bowel disease is slightly lower than that of juvenile rheumatoid arthritis, or approximately 100 cases per 100,000 American children ≤ 16 years, or approximately 70,000 cases (3). Glucocorticoids are likely to be used in a majority of these patients. Other chronic diseases that may require glucocorticoid therapy, such as thrombocytopenic purpura, glomerulonephritis, or pemphigus occur at a much lower frequency.

Bisphosphonates in the Treatment of Glucocorticoid-induced Osteoporosis in Children

Only a few, small, open, mostly short-term studies of pharmacologic approaches to increasing BMD in children have been published. In a study of the effect of pamidronate in the treatment of progressive spinal osteoporosis in 12 children (median duration of therapy 5.2 years), treatment was associated with: 1) a normal pattern of linear growth; 2) marked increases in calcium balance sustained after the first year of therapy; and 3) increases in BMD at both axial and appendicular skeletal sites with a tendency of values to reach normal ranges, especially if treatment was started before puberty. In this study, complete reversal of vertebral deformities was also observed in some prepubertal children, similar to previous reports of improvement of vertebral shape observed in Cushing's disease after successful treatment. It appears that vertebrae in children have the potential to restore their structure as soon as the adverse stimulus is removed or treated, which does not occur in the adult skeleton (8, 9).

To date, there is limited experience on the use of alendronate in children receiving pharmacologic doses of glucocorticoids. However, some preliminary data suggest that alendronate may be beneficial in the treatment of children affected with disorders characterized by increased bone resorption. In a small, non-controlled study, four girls aged 6-13 years, on chronic glucocorticoid therapy for a variety of rheumatic diseases, received two courses of intravenous alendronate at the dose of 3.25 mg/day for 3 consecutive weeks every 3 months. Back pain resolved in all the patients within one week of the first alendronate administration. Clinical improvement was associated with significant increases in lumbar spine BMD after 12 months (average increase of 11.4% from baseline). Growth velocity was not negatively affected during the follow-up period and the treatment was well tolerated by all patients (10).

More recently, the same group of investigators presented preliminary data from a multicenter, open study of oral alendronate in 46 children with rheumatologic diseases (31 females, 15 males), aged 5 to 18 years, receiving glucocorticoid treatment for at least 6 months and with low BMD (at least 2 SD below the normal mean for their age). Oral alendronate was administered at the dose of 5 or 10 mg/day, depending on body weight. After 6 months of treatment, a significant increase in lumbar spine BMD was seen in 20 of 23 (87%) patients. Alendronate was well tolerated (11).

These results, albeit obtained in open studies in a limited number of children, are consistent with the positive effects of alendronate observed in adults (7).

Bisphosphonates for Other Forms of Osteoporosis in Children

In addition to glucocorticoid-induced osteoporosis, bisphosphonates (mainly pamidronate) have been used in other pediatric conditions characterized by bone loss and increased bone fragility, such as osteogenesis imperfecta (9, 12, 13), idiopathic juvenile osteoporosis (9), and juvenile chronic arthritis (eg. rheumatoid) (14). These studies have shown a positive effect to decrease bone turnover and increase bone mass. For example, in an uncontrolled observational study of 30 children aged 3 to 16 who had severe osteogenesis imperfecta, intravenous pamidronate produced a dramatic annualized increase of 42% in lumbar spine BMD, associated with a significant reduction in the incidence of vertebral fractures. The increase in spine BMD was also associated with a 27% increase per year in metacarpal cortical width (12).

The experience obtained with alendronate is more limited. However, preliminary data obtained in an uncontrolled, observational study appear to be quite positive. This study, reported at the recent First International Conference on Children's Bone Health, Maastricht, May 1999, examined the effects of alendronate in 18 children (12 boys and 6 girls), aged 9 to 17, affected with osteoporosis due to a variety of causes (glucocorticoid therapy = 8; juvenile idiopathic osteoporosis = 4; juvenile rheumatoid arthritis = 2; idiopathic hypercalciuria = 2; osteogenesis imperfecta = 2). Children received oral alendronate at doses ranging between 10 mg three times a week and 10 mg daily for up to 18 months. At the end of the observation period, lumbar spine BMD increased significantly, and radial BMD trended in a positive direction. Importantly, the fracture rate decreased from 2.9 to 0.2 fractures/patient/year ($p < 0.05$). Alendronate therapy was also well tolerated (Craig Langman, personal communication).

Safety Issues Specific to the Study Population

Bisphosphonates have been used in small groups of children with metabolic bone diseases including osteogenesis imperfecta, idiopathic juvenile osteoporosis and glucocorticoid-induced osteoporosis (9, 12-14). They have generally been well tolerated with minimal side effects. Specifically, deleterious effects on the growing skeleton have not been observed. Fracture healing has also not been adversely affected.

Bisphosphonates given as intravenous boluses to children prior to closure of the growth plates show characteristic bands of higher bone density at the metaphyses, especially in bones undergoing rapid growth (9). This effect has been described as "undertubulation", and consists of reduced remodeling of the shape of the long bones just below the metaphysis. When treatment is discontinued, remodeling does then occur leaving a normally shaped bone with a dense line of mineralization at the point where the growth plate was being formed during the time of treatment. This radiologic finding is not associated with any known clinical consequences. Skeletal maturation and linear growth proceed normally during treatment. In addition, bone biopsies obtained in children taking bisphosphonates show normal mineralization and lamellar structure (15).

No significant effects on the development of the teeth or dental arch in children have been reported in children treated with bisphosphonates. Delayed dental eruption has been described in newborn rats given subcutaneous pamidronate (at the dose of 1.25 µg/g/day) for 10-15 days; the architecture of these delayed teeth appeared to be normal (16). In contrast, slight disruptions in the formation of enamel and dentin have also been reported with etidronate, consistent with the drug's known effect to impair bone mineralization (17). Delayed eruption of the lower incisors, abnormality in the direction of eruption, and deformation of incisors, have also been reported in the offspring of rats treated with intravenous alendronate at a dose of 1 mg/kg (equivalent to an oral dose of approximately 140 mg/kg), but not at a lower dose of 0.1 mg/kg (18). These findings are unlikely to be relevant in children with the doses proposed for study.

C. Environmental Impact

MRL claims that the Agency action requested in this petition would be subject to a categorical exclusion and would not require a further environmental assessment (EA) or abbreviated environmental assessment (AEA) in accordance with 21 CFR § 25.24(c)(2).

D. Economic Impact

This information will be submitted only when requested by the Commissioner following review of the petition. See 21 CFR § 10.30(b).

E. Certification

The undersigned certifies that, to the best of his/her knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Sincerely yours,

Michele R. Flicker

Michele R. Flicker, MD, PhD
Director, Regulatory Affairs

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Federal Express #1

Desk copy: Dr. Solomon Sobel, HFD-510, Room 14B-04 - Federal Express #2
Mr. Randy Hedin, HFD-510, Room 14B-04 - Federal Express #2

LIST OF REFERENCES*

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18. MRL Nonclinical Pharmacology and Toxicology Documentation, C. Reproductive Toxicity, I. Summary, January, 1994, Reference C-27: Intravenous peri- and postnatal study in rats.

* - All references are available upon request.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on last page.

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Merck & Co., Inc.	7/28/99
TELEPHONE NO. *(Include Area Code)* (610) 397-3193	FACSIMILE (FAX) Number *(Include Area Code)* (610) 397-2516
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: Sumneytown Pike P.O. Box 4 BLA-20 West Point, PA 19486	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 20-560

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
alendronate sodium tablets	FOSAMAX™

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* aminohydroxybutane bisphosphonate

CODE NAME *(If any)* L-670,452

DOSAGE FORM	STRENGTHS:	ROUTE OF ADMINISTRATION:
TABLETS	5mg; 10mg;40mg	Oral

(PROPOSED) INDICATION(S) FOR USE: Treatment and prevention of osteoporosis in postmenopausal women, including prevention of fractures; Treatment of Paget's Disease of Bone

APPLICATION INFORMATION

APPLICATION TYPE (check one) ☐ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

REASON FOR SUBMISSION
Citizen Petition - Pediatric Priority List

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 — THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry Section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Microbiology section (21 CFR 314.50 (d) (4))
	8. Clinical data section (21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (21 CFR 314.50 (f) (1), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k) (1))
	17. Field copy certification (21 CFR 314.5 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
X	19. OTHER (Specify) Citizen Petition - Pediatric Priority 2.5X

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In case of a prescription drug product or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, State and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Michele R. Flicker	Michele R. Flicker, M.D., Ph. D. Director, Regulatory Affairs	7/28/99

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